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Bacterial decontamination of surgical wounds treated with Lavasept®

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Abstract

In a prospective randomized controlled double-blind study in 50 acutely injured patients, bacterially contaminated type 2–4 soft tissue wounds were treated with moist dressings of 0.2% Lavasept® (fractionated polyhexamethylenbiguanide and macrogolum 4000) solution ($n = 28$) in comparison with Ringer solution ($n = 22$). Standardized swabs were taken on days 0, 2, 8 and 15 and investigated for microorganisms. For a quantitative evaluation, the number of colony forming units (CFU) was determined by a serial dilution technique. The tissue compatibility and anti-inflammatory effect were rated on a scale of 0 (= bad) to 3 (= very good). The most frequently found microorganism was *Staphylococcus aureus*, which was isolated from 13 wounds. Use of Lavasept® led to a faster and significant reduction in microorganisms on the wound surfaces. The number of CFU per wound remained constant or decreased, in contrast to the wounds treated with Ringer solution. This was true for both Gram-positive and Gram-negative bacteria. There was no evidence of impaired wound healing in either group. The anti-inflammatory effect and the tissue compatibility of Lavasept® were rated significantly better than that of Ringer solution. It is concluded that Lavasept® combines antiseptic action with good tissue compatibility.

Introduction

New locally applied antiseptics are required urgently from the surgical viewpoint. With Lavasept® concentrate now a microbicidal antiseptic with a broad spectrum of action is available. Clinical experience reports (Roth et al., 1985) and experimental studies in cell cultures and animals (Kallenberger et al., 1991; Werner, 1992; Kramer et al., 1993) show advantages of Lavasept® compared with other antiseptics. The main criticism of the use of antiseptics for treatment of contaminated soft tissue wounds is the impairment of wound healing caused by the toxic properties of wound antiseptics used in the past (e.g. carbolic acid, mercury bichloride, Dakin's solution, hydrogen peroxide, rivanol, etc.) (Schmitt 1981a, b). In the absence of other objective parameters, surgeons generally agree on the importance of clinical evaluation in wound management. However, if only for regulatory reasons, demonstration of a measurable effect of antiseptic wound care must be required as conditio sine qua non. Conduct of

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in vivo clinical studies to prove the efficacy of antiseptic wound care was uncommon in the past, but is generally called for today by critics of new forms of topical antiseptic wound care. So the in vivo effectiveness of Lavasept® solution was investigated in comparison with Ringer solution for the topical treatment of soft-tissue wounds of acutely injured patients. The study was approved by the ethics committees of the participating trial centers and aimed to answer the following questions:

1. Does the use of 0.2% Lavasept® solution lead to a reduction in the bacterial count on the surface of wounds in humans compared with Ringer solution?
2. Does 0.2% Lavasept® solution interfere with wound healing?

Patients and methods

Patients

The prospective, randomized, double-blind study was performed in accordance with the declaration of Helsinki. Fifty acutely injured patients with bacterially contaminated or infected soft tissue wounds were recruited at two study centers (Essen, Duisburg) between 1994 and 1997.

Admission criteria

Patients were admitted to the study with an age over 18 years and a bacterially contaminated or infected soft tissue wound of type 2 (clean contaminated after radical debridement), type 3 (still contaminated) or type 4 (dirty, i.e. purulent wound) (Cruse and Ford, 1980).

Exclusion criteria

Patients were excluded from the study for the following contraindications: irrigation of joints or cartilage, application to the central nervous system, the middle or inner ear or the eye, pregnancy, known hypersensitivity to polyhexamethylene biguanide, uncontrolled diabetes mellitus (blood sugar >300 mg/dl despite insulin therapy), previous antiseptic treatment, use of topical antibiotics, immunosuppression, HIV infection and cortisone therapy.

Study design

After the patients had given informed consent to participation in the study, general baseline data were recorded (age, sex, height, weight, risk factors, erythrocyte sedimention rate, blood count, body temperature, blood pressure, pulse rate). The patients were then allocated to one of the two double-blind treatment groups (Ringer solution or Lavasept® 0,2% solution) by stratified randomization.

The entry examination consisted of clinical evaluation, measurement of the wound area in cm^2 and photographic documentation of the baseline status. A standardized collection of a swab specimen (same investigator using a meandering technique by rolling a cotton swab over the entire wound surface) was taken and the size of the wound was determined by planimetry. After this initial examination, the first moist wound dressing was applied using cotton dressing pads moistened with Ringer or Lavasept® solution in a standardized fashion (10 ml solution per cotton pad).

In the Lavasept® treatment group cotton dressing pads (Lohmann, Neuwied, Germany) moistened with 10 ml 0.2% Lavasept® solution (Fresenius, Bad Homburg, Germany) per single cotton pad were placed directly on the surface of the wound. The colorless Lavasept® solution is a combination of the microbicidal agent polihexanid (20%) and macrogolum (= polyethylene glycol) 4000 (1%) in aqueous solution. The solution for use (0.2%) was fabricated by Fresenius, Bad Homburg, Germany, by adding 2 ml Lavasept® to 1000 ml Ringer solution, giving a dilution of 0.4 mg/ml for the active ingredient polihexanid.

In the Ringer control treatment group, the cotton dressing pads were moistened with sterile Ringer solution (10 ml solution per dressing, Fresenius, Bad Homburg, Germany) and applied in the same manner.

In both groups, the wound dressings were changed completely once a day after moistening and were additionally moistened by the same investigator 12 h later with the identical volume of solution to avoid desiccation of the wound dressing. On days 4, 8, 11 and 15 the wound was evaluated again as described for the entry examination (see above). Photographic evaluation and laboratory tests were also carried out on these days and the patients were asked by the investigator whether they had experienced any discomfort. Deviating from this pattern, bacteriological swab specimens were collected from the wounds on day 2 while the collection on day 4 was omitted. For the purpose of this study the planned maximum duration of treatment of the soft tissue wounds with Lavasept® 0.2% solution or Ringer solution and observation of the wound healing was 15 days as in the case of uncomplicated healing within this time surgical wound closure was considered possible.

In addition, a global subjective evaluation of efficacy and tolerability by the surgeon was analyzed. In particular, any adverse effects of treatment documented and a score for subjective patient discomfort were also recorded. Wound typing (Cruse and Ford, 1980) was performed blindly by an expert panel on the basis of the photographic documentation. Descriptive subgroup analyses were performed separately by center and wound type.

Investigation of bacterial contamination. The swabs were investigated for microorganisms, which were identified by routine procedures. For a quantitative evaluation, the number of colony forming units (CFU) was determined by a serial dilution technique. The cotton tip of the swab was chopped and suspended in 0.85% NaCl solution. A serial 1:10 dilution covering dilutions from 10^1 to 10^6 was performed. An aliquot of 0.5 ml was spread over columbia blood agar plates 8.5 cm in diameter. The plates containing between 30 and 300 CFU were counted after 24 h of incubation at 37 °C and the number of CFU/cm^2 wound surface was calculated.

Rating of anti-inflammatory effect and tissue compatibility. The anti-inflammatory effect and the tissue compatibility were rated on a scale of 0 (= bad), 1 (= moderate), 2 (= good) to 3 (= very good).

Statistical procedure

The patients were allocated to the treatment arms on the basis of a computer algorithm for dynamic randomization, which optimally balanced the distribution of the relevant characteristics like center, inpatient/outpatient treatment, wound area ($<$ or $>10\,cm^2$), wound purulent (yes/no) and antibiotic therapy (i.v. cephalosporine yes/no) in the randomization groups.

Duration of treatment and bacterial contamination were described by Kaplan–Meier estimates. A descriptive comparison was made on the basis of the log-rank test (Kalbfleisch and Prentice, 1980).

The subjective evaluations of efficacy and tolerability on the basis of four ordinal categories, respectively (very good, good, moderate, bad), were compared using the Cochran–Mantel–Haenszel test (Sachs, 1991).

Results

Of 50 patients with bacterially contaminated soft tissue wounds, 28 patients were treated locally with 0.2% Lavasept® solution and 22 with Ringer solution. The distribution of the general patient characteristics age, sex, average age and body surface area determined at the beginning of the study, the baseline parameters wound area, erythrocyte sedimention rate, red blood cell count, white blood cell count, hemoglobin, hematocrit, body temperature, blood pressure, pulse and the criteria for the stratified randomization (antibiotic treatment, inpatient/outpatient treatment, purulent wound infection, wound size $>10\,cm^2$) was balanced between the treatment groups. The median duration of treatment in both groups was 8 days (2–15). Deep infections as a complication of the wound treatment did not occur in either treatment group.

Bacterial contamination

The most frequently found microorganism was *Staphylococcus aureus*, which was isolated from 13 wounds (Table 1). Further isolated microorganisms are listed in the table.

In the patients with initially contaminated wounds, topical wound care with 0.2% Lavasept® solution led to a significantly (log rank test $p = 0.0001$) faster reduction in the bacterial count compared with Ringer solution. Looking at the different wound types, the difference in the reduction of bacterial contamination between both treatment groups was most marked for wound type 2. The treatment of type 2 wounds with Lavasept® did not last longer than until study day 8 in any of the cases.

The total number of CFU per cm^2 wound remained constant or decreased (Fig. 1), in contrast to the wounds

Table 1. Number of different microorganisms per day of investigation and preparation

Microorganism	Day 0		Day 2		Day 8		Day 15	
	L	R	L	R	L	R	L	R
Bacillus spp.	1	1	1	2	1	1	—	—
Enterobacteriaceae	2	3	1	4	—	2	—	1
Neisseriaceae	1	1	2	3	1	2	1	1
Pseudomonas spp.	2	1	1	1	—	1	—	—
P. aeruginosa	1	1	—	1	—	2	—	—
S. aureus	13	5	9	3	5	3	4	1
S. epidermidis	6	6	3	3	—	1	—	1
Streptococcus spp.	—	—	1	1	—	—	—	—
Enterococcus spp.	—	1	—	1	—	1	—	—
Corynebacterium spp.	1	—	—	1	1	2	1	2
None	6	8	14	6	14	3	4	1

L, Lavasept solution group ($n = 28$); R, Ringer solution group ($n = 22$).

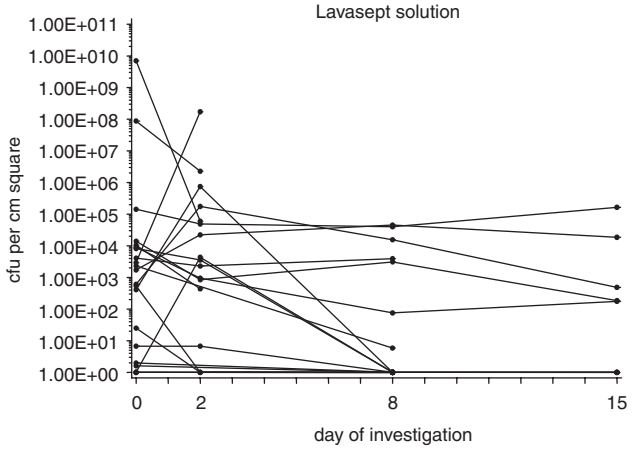

Fig. 1. Bacterial count (cfu) per cm^2 wound surface is reduced significantly faster under wound treatment with Lavasept ($p = 0.0001$, compared with Ringer solution control group).

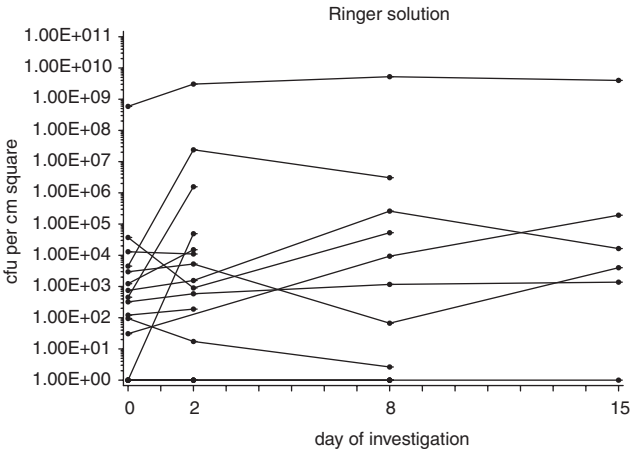

Fig. 2. Bacterial count (cfu) per cm^2 wound surface is not reduced significantly under wound treatment with Ringer solution.

treated with Ringer solution (Fig. 2). This was also true of CFU of single microorganisms per cm^2 wound and both Gram- positive and Gram-negative bacteria.

To represent the efficacy of Lavasept® treatment, all quantitative test results were judged according to the criteria ''pathogens existent'' versus ''pathogens non-existent'' (Table 2). On day 0, under Lavasept® treatment, only 53.8% of all tests were ''non-pathogene'', whereas on day 15 this was the case in 92.3% of all tests. On the contrary, the tests of the group treated with Ringer's solution were 58.3% ''non pathogene'' on day 0 and 83.3% on day 15.

Anti-inflammatory effect

The score for anti-inflammatory effect was very good in 26 (93%) of 28 cases in the Lavasept® group and good or moderate in 1 patient (3.5%). Of the 22 scores in the Ringer group, only 2 (9%) were very good and 13 (59%) good, 4 (18%) moderate and 3 (14%) bad. The double-blind evaluation of the overall efficacy of the test solutions by the investigators shows significantly better results ($p = 0.001$) for Lavasept®.

Table 2. Number of patients with pathogens in the wound (missing examinations = non pathogens)

	Lavasept solution		Ringer solution	
	Count	Col %	Count	Col %
Day 0				
Non pathogen	7	53.8	7	58.3
Pathogen	6	46.2	5	41.7
Total	13	100.0	12	100.0
Day 2				
Non pathogen	8	61.5	6	50.0
Pathogen	5	38.5	6	50.0
Total	13	100.0	12	100.0
Day 8				
Non pathogen	11	84.6	7	58.3
Pathogen	2	15.4	5	41.7
Total	13	100.0	12	100.0
Day 15				
Non pathogen	12	92.3	10	83.3
Pathogen	1	7.7	2	16.7
Total	13	100.0	12	100.0

''count'' = number of wounds.
''col %'' = colonized wounds in relation to total number of wounds.

Tolerability

The local tolerability of the test solutions was evaluated on the basis of the course of the laboratory parameters and the subjective assessment of tolerability by the investigator. The laboratory parameters showed no relevant differences in both groups.

The investigators described 0.2% Lavasept® solution as very well tolerated 27 times (96.5%) and as well tolerated once (3.5%). Ringer solution was described as very well tolerated 11 times (50%), as well tolerated 10 times (45.5%) and as moderately tolerated in one case (4.5%). The difference in the evaluation of tolerability in favor of 0.2% Lavasept® solution is significant ($p = 0.001$).

Discussion

Wound healing and antiseptics

Scientists and surgeons have been searching for an ideal wound antiseptic since the early beginnings of

aseptic surgery. Such a substance should supplement mechanical, surgical wound antisepsis by helping to reduce the bacterial count in any wound.

The longstanding debate about the value of purely mechanical surgical wound debridement versus chemically supported, "adjuvant" surgical wound disinfection still continues, even though the multifactorial etiology of wound infections has been better investigated (Weise and Schäffer, 2000).

The development of infection is determined by the quantity and virulence of pathogenic organisms in relation to the defensive powers of the wound and the organism. While less than 10^5 bacteria/1 g tissue normally is not sufficient to manifest wound infection, the presence of blood, seroma, foreign bodies, earth, non-viable tissue, suture material and immunosuppression lower the bacterial load required for a wound infection (Georgiade et al., 1975). Thus, even after the exhaustion of all mechanical possibilities of wound cleansing available today, e.g., pulsed "jet lavage", and the general establishment of the planned "second look" for further debridement, an empirically derived desire for security still causes many surgeons to wish for additional, adjuvant protection of the patient from manifest wound infection by antiseptics (Edlich et al., 1969).

On account of the known local cytotoxicity of the old antiseptics carbolic acid, sublimate, chlorine-containing solutions, etc., the rise of antibiotics led to a temporary decline in the importance of antiseptics in wound management (Werner and Kramer, 1995; Kramer and Niedner, 1995; Willenegger, 1994).

It was only the worldwide increase in antibiotic resistance that gave rise to a renewed need for agents with good bactericidal action and low tissue toxicity such as povidone iodine and the biguanide solution Lavasept®. When the modern antiseptic Lavasept® was introduced, the requirements for bacteriological proof of efficacy in bacterially contaminated wounds were far more stringent than had ever been the case for antiseptics such as hydrogen peroxide, potassium permanganate, rivanol, mercurochrome, etc., some of which are still widely used today (Kramer, 1995). In addition, in view of the current knowledge in the field of wound healing physiology (Martin and Peacock, 1992; Sedlarik, 1993; Hatz et al., 1993) particular attention must be paid to the tissue compatibility of a new antiseptic in comparison with physiological irrigation solutions (Ringer solution).

Therefore, when discussing the clinical benefit of these improved substances it is important to stress that the desired additional "adjuvant" action of chemical decontamination must not influence observance of the recognized surgical principles of treatment (Schmit-Neuerburg and Kock, 1996). In addition, proof of efficacy must be brought in comparison to the current standard therapy in wound care (i.e. mechanical wound debridement and physiological wound care with Ringer solution, for example). The modern requirements for the efficacy of wound antiseptics further include unambiguous proof of good tissue compatibility, no deactivation by proteins, low toxicity with a low hypersensitization rate, and broad bactericidal, fungicidal and virucidal action (Kramer, 1995).

The target group of our investigation were patients with extensive types 2–4 soft tissue wounds (Cruse and Ford, 1980; Hierholzer and Hierholzer, 1991), a high percentage of which can be assumed to be bacterially contaminated. In spite of the methodological difficulties resulting from the lack of a generally recognized valid parameter for clinical evaluation of wound healing, none of the data in our study (wound score, laboratory parameters, clinical course) revealed any evidence that the use of 0.2% Lavasept® solution interfered with wound healing. On the contrary, at least in some of the wounds, wound healing was improved in comparison with Ringer solution.

On the other hand, after radical debridement and thus the creation of a type 2 wound, there is, particularly in the first 4 days, a significant improvement in wound healing under Lavasept® treatment compared with Ringer solution, which is evidenced by typical, intensely red granulation of the wounds. The pathophysiological processes responsible for these changes in the wound have not yet been investigated in more detail, but further studies using the molecular biological methods available today should be conducted to examine them for the influence of wound healing factors (Vogt et al., 1998; Weise and Schäffer, 2000).

It would be particularly interesting to find out which parameters can be used to further objectify the significant improvement in wound healing by Lavasept®, which we determined here by double-blind comparison. Further studies are also needed to establish which of the two active components (biguanide or macrogolum) is responsible for this established promotion of wound healing.

Bactericidal action of Lavasept®

The present study confirmed the marked statistically significant reduction in the bacterial count ($p = 0.0001$) by Lavasept® solution compared with Ringer solution. The most marked reduction in bacterial contamination was seen in type 2 wounds.

Biguanides of the polyhexamethylene biguanide hydrochloride (PHMB) type were originally developed as surface disinfectants in the food and beverages industry, as their good topical bactericidal action and low toxicity meant that they were able to cover a broad antimicrobial spectrum. For antiseptic wound care, the addition of polyethylene glycol (macrogolum) was considered beneficial as this substance lowers the surface tension of

the solution and thus improves the wetting of wound surfaces (Willenegger, 1994). In microbiological and clinical studies, 0.1% and 0.2% solutions were used. With regard to the bactericidal action of biguanides it is known that the cationic charge of the biguanides leads to direct contact with anionically charged bacteria, which causes rupture of the internal bacterial membranes and denaturation of the protein structures and cell organelles (Schäfer, 1974; Ikeda et al., 1984a, b; McDonnell and Russel, 1999).

In vitro measurements with a bacterial load of 10^8/ml 0.2% solution of Lavasept® led to complete destruction of the organisms *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella* and *Enterobacter* spp. after 5 and 10 min (Werner, 1992). Measurements of the bactericidal action of Lavasept® solution with 0.2% albumin showed only a prolongation of the time required to achieve the same reductions in the bacterial count (Werner and Kramer, 1995).

Tissue compatibility

Apart from the bactericidal action, good tissue compatibility and low toxicity are further critical outcome factors for a positive benefit-to-risk analysis of modern wound antiseptics (Kramer et al., 1993; Hatz et al., 1993). Numerous in vitro investigations and animal studies showed that the tissue compatibility of Lavasept® is comparable to that of Ringer solution (Kallenberger et al., 1991; Kramer et al., 1993; Kramer and Adrian, 1996; Niedner, 1996).

In recent animal studies, various antiseptics (Lavasept® 0.1% and 0.2%, Taurolin 0.5% and 2%, Betadine; chlorhexidine, Octenisept, alcohol 70% and 80%, isopropyl alcohol 60%) were also compared in a model for deep or non-healing chronic wounds (Kramer et al., 1998). Lavasept® 0.2% solution was amongst the antiseptics with the most favorable results for tissue compatibility in deep and non-healing wounds.

Our own evaluation of the tissue compatibility in soft tissue wounds in humans confirms this rating of the 0.2% Lavasept® solution, which was significantly superior to Ringer solution. This supports other clinical reports (Roth et al., 1985; Willenegger, 1994; Schmit-Neuerburg and Kock, 1996; Schmit-Neuerburg et al., 2001), although the finding that the tissue compatibility was better than that of Ringer solution was surprising. One reason for this may be the rapid promotion of red granulation tissue which has already been described for Lavasept® (Schmit-Neuerburg and Kock, 1996).

Conclusions

The aim of the present study was to answer some outstanding microbiological questions on the clinical value of the novel antiseptic Lavasept®. The results obtained confirm the following issues:

1. In the management of surgically radically debrided but still bacterially contaminated soft tissue wounds Lavasept® can lead to faster and significant reduction of microorganisms on wound surfaces in comparison with Ringer solution.
2. Application of the novel antiseptic Lavasept® to bacterially contaminated soft tissue wounds does not lead to the impairment of wound healing described after use of older antiseptics.
3. In this double-blind evaluation 0.2% Lavasept® solution was significantly better rated in regards to tissue compatibility than Ringer solution.
4. The qualitative and quantitative microbiological investigations indicate the good antimicrobial action of Lavasept® treatment in comparison to control treatment with Ringer's solution.
5. It is concluded that Lavasept® combines antiseptic action with good tissue compatibility.

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